Case Report

Epidermodysplasia Verruciformis Associated with Peripheral T-cell Lymphoma, Squamous Cell Carcinoma, and Langerhans Cell Histiocytosis

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Abstract

Epidermodysplasia verruciformis (EV) is an extremely rare autosomal recessive genodermatosis characterized by abnormal susceptibility to human papilloma virus (HPV) infection. The inability to terminate HPV infection leads to widespread and persistent wart-like and macular skin lesions. The extent of cutaneous inivolvement and progress of the lesions vary considerably, but the persistence of skin lesions throughout the life is a characteristic feature of EV. The interaction among potentially oncogenic HPV genotypes, ultraviolet radiation, altered immunity, and genetic factors will lead to the development of nonmelanoma skin cancers in 30%–60% of cases. Although there is lifelong increased risk of squamous cell carcinoma, the association with hematological or solid malignancies is rare. Literature search shows very few isolated reports of non-Hodgkin's lymphoma, astrocytoma, thymoma, adenocarcinoma intestine, and leiomyosarcoma in patients with EV. Herein, we report a case of EV with an uncommon occurrence of peripheral T-cell lymphoma, squamous cell carcinoma, and Langerhans cell histiocytosis. EBV-associated squamous cell carcinoma carries increased number of viral proteins and this may play role in cell immortalization, chromosomal destabilization, and activation of telomerase. The development of lymphoma and Langerhans cell histiocytosis may be due to the defect in immune system and due to the oncogenic potential of the virus. These point to the importance of regular long-term follow-up of EV patients for the possible cutaneous and extracutaneous malignancy.

Keywords: *Epidermodysplasia verruciformis, langerhans cell histiocytosis, squamous cell carcinoma, T-cell lymphoma*

Introduction

Epidermodysplasia verruciformis (EV) was first described by Lewandowsky and Lutz in 1922. These patients develop immunological tolerance, i.e., inability to recognize and reject human papilloma viruses (HPVs) which will lead to the development of viral-induced lesions. EV is characterized by the occurrence of polymorphous skin lesions. The affected individuals have lifelong increased risk of squamous cell carcinoma, particularly in sun-exposed areas. Only few isolated cases of extracutaneous malignancies are reported in EV patients.

Case Report

A 28-year-old male patient presented with rapidly enlarging swelling in the left eyelid with associated itching for 2 months. He had a history of nodular and scaly lesions in the skin, especially over palms and feet for the past 8 years. The patient was seronegative for human immunodeficiency virus.

On examination, there were multiple verrucous and nodular lesions in the hand and feet and scaly lesions all over the body [Figure 1a and b]. A 4 cm × 4 cm swelling with skin ulceration over the left eyelid which was obscuring vision was noted [Figure 2a]. Blood counts were within normal limits. CT scan showed irregular thickening over the skin of left eyelid with soft tissue mass measuring 4.7 cm × 2.4 cm. Bilateral-level four cervical lymph nodes (largest measuring 2.1 × 1 cm), left axillary node (measuring 2 × 2 cm), and bilateral inguinal nodes (largest measuring 1.7 × 0.8 cm) were noted. Biopsy of the swelling over the eyelid and the skin lesion was taken from an outside center. The skin lesion was diagnosed as EV. We reviewed the slides, and immunohistochemical examination was done on the blocks.

How to cite this article: Sukumaran R, Nair RA, Jacob PM, Vasudevan JA. Epidermodysplasia verruciformis associated with peripheral T-cell lymphoma, squamous cell carcinoma, and Langerhans cell histiocytosis. Clin Cancer Investig J 2017;6:174-7.

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Access this article online

Website: www.ccij-online.org

DOI: 10.4103/ccij.ccij_37_17

Quick Response Code:

Histopathological examination of the skin lesions showed hyperkeratosis, acanthosis, and hypergranulosis [Figure 1c and 1d]. Correlating the history and clinical picture, the microscopic findings were compatible with EV.

Biopsy from the lesion over the eyelid showed sheets of neoplastic cells beneath intact squamous epithelium. The cells were small- to medium-sized with irregular nuclei [Figure 2b]. On immunohistochemical examination, the atypical cells were CD3 positive and CD5 positive and showed loss of CD7 [Figure 2c and d]. The neoplastic cells were CD20 negative and Tdt negative. Based on the morphology and immunoprofile, a diagnosis of peripheral T-cell lymphoma was given.

Excision biopsy of the axillary lymph node was done. Microscopy showed preserved architecture of the node with sinusoidal and paracortical collections of large cells with grooved nuclei admixed with scattered eosinophils [Figure 3a]. On immunohistochemical examination, these atypical cells were positive for S100 and CD1a [Figure 3b]. A diagnosis of Langerhans cell histiocytosis involving lymph node was given.

Palliative radiotherapy was given for the lesion in eyelid following which the lesion considerably reduced in size. Eight months later, the patient came with an ulceroproliferative lesion in the scrotum and another lesion in the abdominal wall. The lesion of the scrotum measured 4 cm × 4 cm and was extending to the root of the penis [Figure 4a]. Biopsy of the scrotal lesion revealed squamous cell carcinoma. Wide excision of the lesion was done which showed moderately differentiated squamous cell carcinoma with extensive perineural tumor infiltration [Figure 4b].

Wide excision of the lesion over the abdominal wall showed sheets of neoplastic small- to medium-sized cells with irregular nuclei [Figure 5a]. The atypical cells were positive for CD3 [Figure 5b] and were Tdt negative. A diagnosis of peripheral T-cell lymphoma was made.

Discussion

EV is an extremely rare genetic hereditary skin disorder characterized by highly polymorphic cutaneous lesions. The disease is characterized by an unusual susceptibility to certain HPV including HPV types 5, 8, 9, 12, 14, 15, 17, 19, 25, 36, 38, 47, and 50, collectively known as EV-HPV.[1] The uncontrolled HPV infections can lead to the growth of wart-like papules and may vary from macules, hyperkeratotic papules to exophytic cauliflower-like masses. The lesions commonly develop in the hands

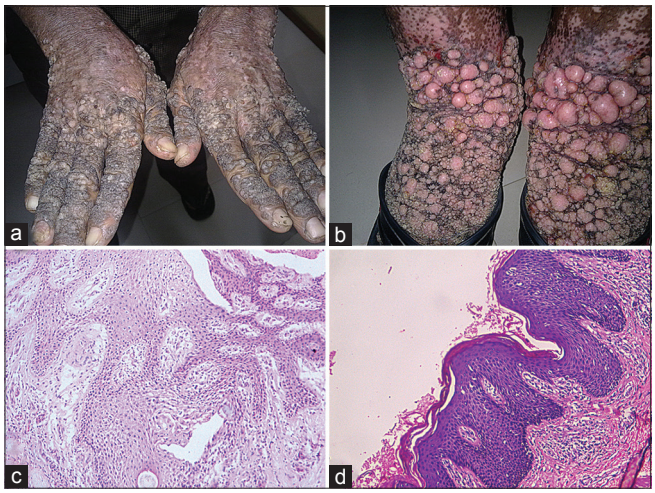

Figure 1: (a) Verrucous lesions hand. (b) Nodular and verrucous lesions feet. (c) Microscopy showing acanthosis, hypergranulosis, and hyperkeratosis (H and E, ×100). (d) Microscopy showing mild dysplasia (H and E, ×200)

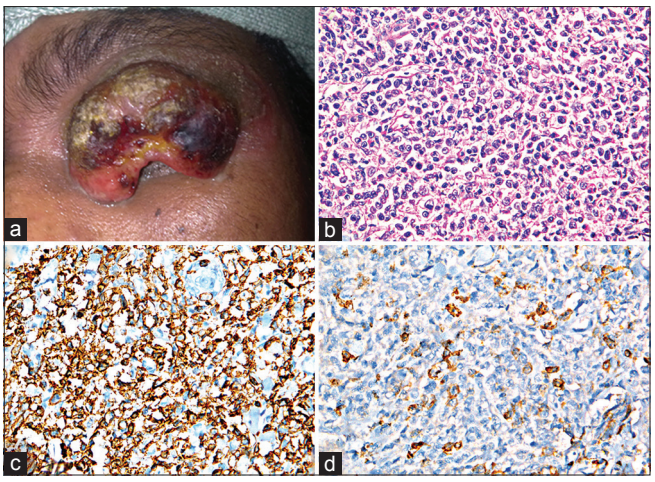

Figure 2: (a) Lesion over the eyelid. (b) Microscopy showing diffusely arranged atypical small- to medium-sized cells (H and E, ×200). (c) Neoplastic cells are CD3 positive (immunohistochemistry, ×200). (d) Neoplastic cells with loss of CD7 (immunohistochemistry, ×200)

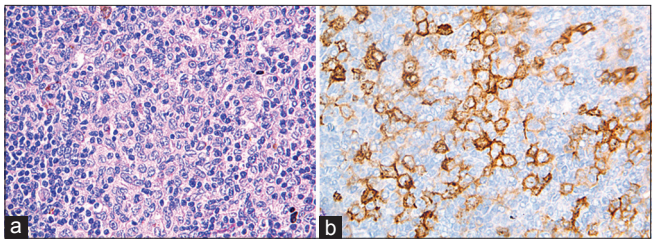

Figure 3: (a) Lymph node showing paracortical collections of large atypical cells with grooved nuclei (H and E, ×200). (b) The large atypical cells are CD1a positive (immunohistochemistry, ×400)

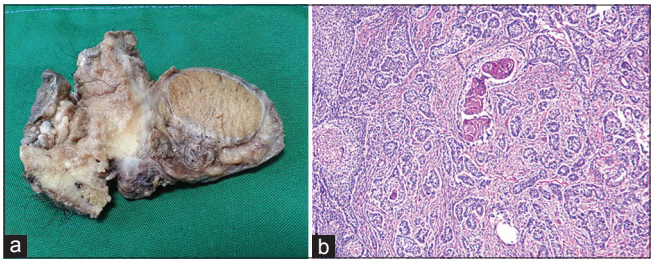

Figure 4: (a) Ulceroproliferative lesion scrotum. (b) Microscopy showing squamous cell carcinoma (H and E, ×200)

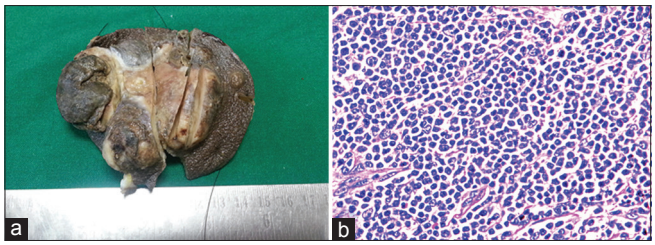

Figure 5: (a) Lesion abdominal wall. (b) Microscopy showing diffusely arranged small- to medium-sized atypical cells with irregular nuclei (H and E, ×200)

and feet. Among the EV-type HPVs, HPV 5 and 8 have oncogenic potential.

Two EV susceptibility loci, EV1 and EV2, were discovered on chromosome 17 and 2. EVER 1 and EVER 2 genes located in the EV1 locus belong to the transmembrane channel-like gene family and may serve as restriction factors for EV HPVs.[2] The mutation and malfunctioning of these genes will cause a defective cell-mediated immunity against specific types of viruses.[3]

On microscopic examination of the skin, there will be enlarged cells in the granular/spinous layer with distinctive blue-gray swollen cytoplasm. Keratohyaline granules and koilocytotic atypia can been seen.

Epidermodysplasia verruciformis and squamous cell carcinoma

The disseminated verrucous lesions in EV develop from childhood and persist lifelong. The malignant changes in these lesions usually start between 20 and 40 years of age.[4] Nonmelanoma skin cancers occur in 30%–60% patients, especially squamous cell carcinoma, mainly in the sun-exposed areas. Transformation of benign lesions to malignancy is proportional to the amount of sunlight exposure. The HPV subtypes 5, 8, and 47 are closely associated with malignant lesions. EV squamous cell carcinoma harbor high copy numbers of episomal HPV genomes and abundant transcripts of E6 and E7 genes. These viral proteins play role in cell immortalization, chromosomal destabilization, and activation of telomerase.[5] These effects of the oncogenic viruses along with other cofactors, such as ultraviolet irradiation and decreased cell-mediated immunity, can result in the malignant transformation of cutaneous benign lesions.

The pathogenesis of noncutaneous malignancies in patients with EV is not fully understood. Few isolated cases of non-Hodgkin lymphoma, thymoma, leiomyosarcoma, adenocarcinoma, and astrocytoma are reported in patients with EV.[6-9]

Epidermodysplasia verruciformis and non-Hodgkin lymphoma

Association between lymphoma and EV is not well documented. The oncogenic properties of HPV viruses such as cell immortalization, chromosomal destabilization, and activation of teromerase may play roles in the development of lymphoma. Expression of lymphomagenic oncogenes in T-cell lymphomas of HPV16 transgenic mice supports the theory of lymphomagenic effects of some HPV subtypes.[10]

Innate immunity is essential for the prevention and control of HPV infection. Patients with EV will have defective innate immunity which in turn results in persistent infection with HPV. Lymphomas are more common in immunosuppressed patients.[11] Some researchers point to the fact that the immunosuppressive background is responsible for the development of lymphoma in EV patients.

Genetic defects may be another possible cause of lymphoma in EV patients. EV is an autosomal recessive disorder, the genetic causes of which are still unclear. Genetic defects are widely described in lymphomas. The same genetic alterations which play major roles in the development of EV may lead to the development of lymphoma.[6-9]

Epidermodysplasia verruciformis and Langerhans cell histiocytosis

Langerhans cell histiocytosis is a rare systemic disease associated with proliferation and accumulation of cells with surface markers similar to cutaneous Langerhans cell. Function of the Langerhans cells is to capture antigens and present them to lymphocytes and is considered as an immune system accessory cell. Langerhans cell histiocytosis occurs mainly in children between 1 and 4 years. Its occurrence in adults is quite rare. The exact cause of the disorder is not known. The possible causes suggested by the researchers include infections or abnormalities of the immune system but are yet to be proved. Some lymphomas and sarcomas showing clusters and sheets of Langerhans cells are reported. It is yet to be proved whether this is a local reactive phenomenon or a transdifferentiation process.[12] In our case, there were focal collections of Langerhans cells in the node and this may be due to the abnormalities in the immune system.

Conclusion

EV is an extremely rare genodermatosis characterized by polymorphous skin lesions. Increased susceptibility and lifelong persistence of specific HPV infections result in an increased risk for the development of carcinoma of the skin, particularly in sun-exposed areas, at a younger age than the general population. Our case shows the development of squamous cell carcinoma (in the genital region), peripheral T-cell lymphoma (at multiple sites), and Langerhans cell histiocytosis (involving lymph node at the age of 28) in an EV patient. The lifelong persistence of infection can lead to malignancies due to cell immortalization, activation of telomerase, and chromosomal destabilization. Immunodeficiency to viral antigens can eventually lead to cancer. These point to the

need for long-term close follow-up of the EV patients for cutaneous and extracutaneous malignancies.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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